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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,430	BOHMER, RALPH M.	
	Examiner	Art Unit	
	GAILENE R. GABEL	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,58 and 68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15, 58, and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed March 31, 2009 is acknowledged and have been entered. Claim 58 has been amended. Claims 59-67 have been cancelled. Accordingly, claims 1-15, 58, and 68 are pending and are under examination.

Withdrawn Rejections / Objections

2. All rejections or objections not reiterated herein, have been withdrawn.

3. The rejections of claims 59-67 are now moot in light of Applicant's cancellation of the claims.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-15, 58 and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in being incomplete for omitting essential structural and functional cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. In this case, the preamble recites. "A method of identifying a fetal cell in a maternal blood sample";

whereas, the method concludes with step b) which recites, "detecting a maternal antibody bound to paternally inherited fetal antigen on a fetal cell." Accordingly, it is unclear as to whether the method intends merely "identifying a fetal cell" or "detecting maternal antibody which has bound to paternally inherited fetal antigen on fetal cell." Specifically, claim 1 fails to clearly define that the fetal cell intended to be identified is that which carries a paternally inherited fetal antigen upon which a maternal antibody has bound.

Claim 1 is also indefinite in being incomplete in failing to specifically recite what elements are required to effect detection and how detection of the maternal antibody bound to paternally inherited fetal antigen on a fetal cells is performed.

Claim 1 is also indefinite in being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. In this case, it is unclear how the maternal antibody is detected, absent incorporation of a detection label that defines differential binding of the maternal antibody to the paternally inherited fetal antigen on the fetal cell.

In as far as the missing elements and structural relationships in claim 1 which are disclosed in the specification, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim 2 is also confusing because it recites, "further comprising exposing the maternal antibody bound to a fetal cell to an agent capable of forming a complex with the maternal antibody" which appears to intend to label the antibody intended to be

detected; however, claim 1 from which it depends appears to have already performed a detection step to detect the maternal antibody, albeit ambiguously so.

The term "exposing [an agent]" and the recitation of "an agent capable of forming a complex" in claim 2 is indefinite because it is unclear how an actual positive complex formation is effected absent 1) definite contact of the exposed agent to the maternal antibody; and 2) definite binding and complex formation of the agent with the maternal antibody. As recited, the agent is only merely exposed and capable of forming a complex with maternal antibody.

Claim 5 is indefinite in being incomplete for omitting essential structural and functional cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. In this case, the preamble recites. "A method of identifying a fetal cell in a [any] sample"; whereas, the method concludes with a step which recites, "detecting a maternal antibody bound to a fetal cell, wherein the maternal antibodies comprise maternally produced antibodies specific for paternally inherited fetal antigens." Accordingly, it is unclear as to whether the method intends merely "identifying a fetal cell in a sample" or "detecting maternal antibody which has bound to fetal cell carrying paternally inherited fetal antigen." Specifically, claim 5 fails to clearly define that the fetal cell intended to be identified is that which carries a paternally inherited fetal antigen upon which maternal antibodies bind to.

Claim 5 is also indefinite in being incomplete in failing to specifically recite what elements are required to effect detection and how detection of the maternal antibody bound to paternally inherited fetal antigen on a fetal cells is performed.

Claim 5 is also indefinite in being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. In this case, it is unclear how the maternal antibody is detected, absent incorporation of a detection label that defines differential binding of the maternal antibody to the paternally inherited fetal antigen on the fetal cell.

In as far as the missing elements and structural relationships in claim 5 which are disclosed in the specification, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim 5 is also confusing because it recites, "exposing cells in the sample to maternal antibodies" because it is unclear how binding and detection is effected or performed, absent actual contact of the exposed cell in the sample with the maternal antibodies. As recited, the cell in the sample is merely exposed to maternal antibodies and not directly contacted.

The term "exposing the maternal antibody bound to a fetal cell to an agent" and the recitation of "an agent capable of forming a complex with the maternal antibody" in claim 7 is indefinite because it is unclear how an actual positive complex formation is effected absent 1) definite contact of the exposed agent to the maternal antibody bound to a fetal cell; and 2) definite binding and complex formation of the agent with the

maternal antibody. As recited, the agent is only merely exposed and capable of forming a complex with maternal antibody. See also claim 14.

Claim 58 is indefinite in being incomplete for omitting essential structural and functional cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. In this case, the preamble recites. "A method of identifying a fetal cell in a maternal blood sample"; whereas, the method concludes with step iv) which recites, "detecting a maternal antibody bound to paternally inherited fetal antigen on a fetal cell", and step v) which recites "recovering the fetal cells." Accordingly, it is unclear as to whether the method intends merely "identifying a fetal cell" or "detecting maternal antibody which has bound to paternally inherited fetal antigen on fetal cell." Specifically, claim 58 fails to clearly define that the fetal cell intended to be identified is that which carries a paternally inherited fetal antigen upon which a maternal antibody has bound to.

Claim 58, in steps ii) and iii) is confusing because it is unclear how "the fetal cells from the fraction comprising PBMC from the sample, that are bound to maternal antibodies" are specifically selected to be contacted with an agent that forms a complex with maternal antibodies, whereas it appears that it is the agent that forms a complex with the maternal antibodies so as to allow identification and selection of the fetal cells." It appears that step iii) should instead recite, "contacting the PBMC from step ii) with an agent that forms a complex with the maternal antibodies that are bound to paternally inherited fetal antigen on fetal cells" so as to effect "detection" of fetal cells in step iv).

The recitation of "an agent capable of forming a complex" in claim 58, step iii) is also indefinite because it is unclear how an actual positive complex formation and detection are effected and performed, absent definite binding and complex formation of the agent with the maternal antibody. As recited, the agent is only merely capable of forming a complex with maternal antibody.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 5, 7-9, 11-13, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Warwick et al. (Detection strategy for maternal antibodies against paternal HPA-1 antigen, The Lancet 344: page 64 (July 2, 1994)).

Warwick et al. teach a method comprising obtaining amniotic fluid sample containing one or more fetal cells which carry a paternally inherited fetal antigen (HPA-1), and detecting maternal antibodies that bound to the paternally inherited fetal antigen. Detection of fetal susceptibility to the maternal antibodies can be performed using immunofluorescence testing whereupon the fetal cells are contacted with a detectably labeled agent that forms a complex with the maternal antibody that is bound to paternally inherited fetal antigen (see entire document on page 64, column 2).

Since claim 5 fails to define that the sample is a maternal blood sample; and further fails to define how the maternal antibodies against the fetal cells carrying the paternally inherited HPA-1 antigen are detected; and lastly fails to define that the labeled agents intended for detection of the maternal antibodies are specifically contacted with the cell sample to specifically form a complex with the maternal antibodies against the fetal cells carrying the paternally inherited HPA-1 antigen; it is deemed that the teaching of Warwick et al. reads on the claimed invention.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-15, 58, and 68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a method of identifying and enriching fetal cells carrying a paternally inherited fetal HLA antigen using purified maternal antibodies that are dissociated and extracted specifically from complexes formed with known HLA antigens in maternal plasma deemed to be HLA antigens inherited paternally, does not reasonably provide enablement for the claimed method using generic maternal antibodies or maternal antibodies from any maternal plasma sample dissociated from all complexes formed with soluble HLA antigen and/or anti-idiotypic antibody. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

the specification for the claimed method to work using purified maternal antibodies that are dissociated and extracted specifically from complexes formed with known HLA antigens in maternal plasma deemed to be HLA antigens inherited paternally. However, the specification fails to provide guidance to enable the claimed method to function in exclusively detecting and identifying the fetal cells using antibodies from any maternal plasma sample dissociated from all complexes formed with soluble HLA antigen and/or anti-idiotypic antibody, as claimed.

As set forth in In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a method for identifying and enriching fetal cells from maternal blood, wherein the fetal cells identified are those that carry paternally inherited fetal antigens. These fetal cells are identified by isolating, and purifying maternal antibodies that bind to paternally inherited fetal antigens present in fetal cells so as to form fetal cell-maternal antibody complexes upon contact with the

cell sample, and then detecting the maternal antibodies that bind to or are bound to the paternally inherited fetal antigens on the surface of the fetal cells. The maternal antibody-bound fetal complexes are identified using a secondary antibody or other molecule that binds to the maternal antibody.

The state of the prior art- the prior art of record fails to disclose a method for identifying and enriching fetal cells from maternal blood sample which carry paternally inherited fetal HLA antigen using any maternal antibody that binds to fetal cell or maternal antibodies that bind to or are bound to the paternally inherited fetal HLA antigen on the surface of the fetal cell.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that the claimed fetal cells can be detected by way of maternal antibody bound thereto, considering the problem of scarcity of such fetal cells in maternal circulation, absent isolation procedure for maternal antibodies that bind to paternally inherited fetal HLA antigen on the surface of fetal cells and enrichment procedure of these fetal cells. There is also no predictability based on the instant specification that the claimed "maternal antibodies" would bind exclusively to paternally inherited fetal HLA antigen present on fetal cells, absent isolation and use of purified maternal antibodies that are dissociated and extracted specifically from complexes formed with known HLA antigens in maternal plasma deemed to be HLA antigens inherited paternally.

The amount of direction or guidance present- appropriate guidance is provided in the specification for the claimed method to work using purified maternal antibodies that

are dissociated and extracted specifically from complexes formed with known HLA antigens in maternal plasma deemed to be HLA antigens inherited paternally. However, the specification fails to provide guidance to enable the claimed method to function in exclusively detecting and identifying the fetal cells using antibodies from any maternal plasma sample dissociated from all complexes formed with soluble HLA antigen and/or anti-idiotypic antibody, as claimed.

The presence or absence of working examples- working examples are provided in the specification that show using purified maternal antibodies that are dissociated and extracted specifically from complexes formed with known HLA antigens in maternal plasma deemed to be HLA antigens inherited paternally. There are no working examples that show analogous results using antibodies from any plasma sample dissociated from all complexes formed with soluble HLA antigen and/or anti-idiotypic antibody, as claimed.

The breadth of the claims- as recited, the instant claims are directed to a method for identifying and enriching fetal cells from maternal blood, wherein the fetal cells identified are those that carry paternally inherited fetal antigens. These fetal cells are claimed to be identified by detecting maternal antibodies that bind or are bound to the paternally inherited fetal antigens present in the cells. As recited, antibodies from any plasma sample dissociated from all complexes formed with soluble HLA antigen and/or anti-idiotypic antibody can be used as "maternal antibody" that is detected to be bound to fetal cells.

The invention is drawn to a method for identifying and enriching fetal cells from maternal blood, wherein the fetal cells identified are those that carry paternally inherited fetal antigens. These fetal cells are identified by detecting maternal antibodies that bind or are bound to the paternally inherited fetal antigens present in the cells which are then manifested in the form of fetal cell-maternal antibody complexes. The reagent used to detect, identify, and isolate the fetal cells are maternally-produced antibodies that are specific for the paternally inherited fetal antigens on the fetal cells (page 2, fourth full paragraph).

Applicant provides in page 2, last full paragraph to entire page 3 and page 6, sixth full paragraph, that in the course of a normal pregnancy, the mother mounts a humoral immune response against paternally inherited fetal antigens. A complex network of anti-HLA antibodies, anti-anti HLA antibodies, and soluble HLA antigens exist in maternal plasma; hence, maternal antibodies can bind specifically to fetal cells expressing paternally inherited HLA antigens. The paternally inherited fetal antigens are unique markers which are targeted for isolation and enrichment of fetal cells from maternal blood, resulting to at least a 10-fold increase in fetal cells relative to maternal cells.

Applicant's disclosure at page 6, last full paragraph provides that the maternal antibodies are bound to fetal cells (in vivo) at time of blood collection due to fetal cell exposure to maternal plasma at the time the fetal cells cross-over into maternal plasma. Alternatively, maternal antibodies may also be bound in vitro by contacting cells derived from maternal PBMC with antibody-containing fraction of maternal plasma for a time

and under conditions sufficient to permit formation of maternal antibody-bound fetal complexes (page 7, second and third full paragraph). Applicant then discloses that the maternal antibodies that comprise the maternal antibody-bound fetal cell complexes to be detected and identified are those that are specific for paternally inherited fetal antigen present in the fetal cells, and they are identified using a secondary antibody or other molecule or "isolatable agent" that is capable of binding to the maternal antibody (page 7, second, third, and fourth full paragraph).

The claims specifically recite that maternal antibody [specifically] binds to or is bound to paternally inherited fetal antigen present in fetal cells and it is that maternal antibody bound to paternally inherited fetal antigen present in fetal cells that is detected and identified in the claimed method.

In page 12, first full paragraph of Applicant's disclosure, these antigen reactive antibodies which bind specifically to maternal antibodies against paternally inherited fetal antigen present on the surface of fetal cells, are preferably dissociated from a complex with a soluble HLA antigen and/or an anti-idiotypic antibody present in maternal blood or plasma; the antibody is extracted to form antibody preparation that is partially purified or purified free of antigens. In page 13, second and third full paragraph, Applicant discloses that the maternal antibodies (maternally produced antibodies) specific for paternally inherited fetal antigens are enriched before use in Applicant's method. Enrichment is performed by contacting isolated maternal antibodies to a large panel of HLA antigens bound to solid support, and antibodies that bind to known HLA antigens are separated. Applicant states that since it is highly

unlikely that there are only a few if any, maternal antibodies that bind to maternal HLA antigen, most of the HLA antibodies that are bound are specific for HLA antigens inherited from the father, i.e. or maternal antibodies specific for paternally inherited fetal HLA antigens. If the HLA type of the mother and the father are known, the large panel of HLA antigens in the purification step is preferably selected to exclude maternal HLA antigens and to preferably comprise of paternally-derived HLA antigens.

In page 14, fourth full paragraph the agent disclosed that is intended to bind maternal antibodies bound to fetal cells carrying paternally inherited fetal HLA antigens are antibodies or fragments thereof that bind generally to human antibodies or polypeptides that bind human antibodies such as protein A, protein G, and protein L, and deemed to be isolatable. Human antibodies encompass all of anti-human IgG, IgM, and all other immunoglobulins.

The fact that the claimed method may appear to work based on proof of principle that it is unlikely that there are maternal antibodies that bind to maternal HLA antigens, it is not sufficient to enable the breadth of the claimed invention. While it is not necessary to show working examples for every possible embodiment, there should be sufficient teachings in the specification that would suggest to the skilled artisan that the breadth of the claimed method is enabled. This is not the case in the instant specification.

Applicant's invention is enabled for a method for identifying and enriching fetal cells from maternal blood, wherein the fetal cells identified are those that carry paternally inherited fetal antigens. These fetal cells are identified by detecting maternal

antibodies that bind or are bound to the paternally inherited fetal antigens present in the cells which are then manifested in the form of fetal cell-maternal antibody complexes. The maternal antibody-bound fetal complexes are identified using antigen reactive antibodies which bind specifically to maternal antibodies against paternally inherited fetal antigen present on the surface of fetal cells. The maternal antibodies (maternally produced antibodies) specific for binding paternally inherited fetal antigens are first enriched before use in Applicant's method by subjecting them to a large panel of HLA antigens bound to solid support whereupon the antibodies that bind to known HLA antigens are separated and isolated as paternal specific for use in Applicant's method because there are only a few if any, maternal antibodies that bind to maternal HLA antigen.

Patent protection is granted in return for enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1996), stating in context of the utility requirement that "a patent is not a hunting license. It is not a reward for the search, but for compensation for its successful conclusion." Tossing out the mere germ of an idea does not constitute an enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by the inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Genentech Inc. v. Novo Nordisk A/A (CAFC) 42 USPQ2d 1001.

Response to Arguments

7. Applicant's arguments with respect to claims 1-15, 58, and 68 have been considered but are moot in view of the new grounds of rejection.

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GAILENE R. GABEL whose telephone number is (571)272-0820. The examiner can normally be reached on Monday, Tuesday, Thursday, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

June 9, 2009